Citation:

Nguyen ND, Center JR, Eisman JA, Nguyen TV. Bone loss, weight loss, and weight fluctuation predict mortality risk in elderly men and women. *J Bone Miner Res.* 2007 Aug;22(8):1147-54.

PubMed ID: 17635040

Study Design:

Longitudinal Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

The researchers hypothesized that, in addition to low BMD, the rate at which BMD loss, weight loss, and weight fluctuation are independent risk factors for mortality in the elderly. This study was designed to test the hypothesis by assessing the independent association between bone loss, weight loss, and weight fluctuation in the prediction of all-cause mortality risk in elderly men and women.

Inclusion Criteria:

- Only individuals who had at least three BMD measurements were included in this analysis.
- >= 60 years of age (as of 1989)
- Fractures were included only if the report of fractures was defined and, on interview, had occurred with minimal trauma (e.g., fall from standing height or less).
- The study protocol was approved by the St Vincent's Hospital Ethics Committee.
- All participants gave written informed consent.

Exclusion Criteria:

- Fractures clearly caused by major trauma (as motor vehicle accidents) or underlying diseases (such as cancer or bone-related diseases) or digit or skull fractures were excluded from the study.

Description of Study Protocol:

Recruitment

The recruitment strategies were not detailed. This study was part of the on-going Dubbo

Osteoporosis Epidemiology Study, a longitudinal study, population-based study of risk factors for fracture and mortality.

Design: Longitudinal cohort study

Blinding used (if applicable): not applicable

Intervention (if applicable): not applicable

Statistical Analysis

- The incidence of all-cause mortality was calculated as the number of deaths per 1,000 person-years for the population at risk assuming that the occurrence of death followed the Poisson distribution.
- The study period used in the calculation of person years was defined as the interval between the baseline and follow-up visits, or in the case of death, between baseline and date of death.
- The annual percentage change in BMD and body weight was calculated for each individual using linear regression. In this approach, a linear regression equation was fitted to each individual's data, from which the intercept and slope for the individual was obtained. The percentage of change was estimated as the ratio of slope over the intercept.
- Weight fluctuation can be quantified by two measures: the CV and the residual mean square error (RMSE) that is obtained from the linear regression model of each individual. In this study, two measures were highly correlated, with the correlation coefficient being 0.93. therefore, in this study, CV was used as a measure of weight fluctuation. Specifically, the mean and SD of weight were estimated from multiple measurements of weight, and the CV was estimated from multiple measurements of weight, and the CV was estimated as the ratio of SD over the mean. In preliminary analysis, the SD of weight fluctuations was-3%; therefore, this value as used as a cut-off value to nominally define the stability of weight.
- Cox's proportional hazards regression model was used to estimate relative hazard and 95% CI for each SD or unit change or in specified groups compared with reference group with categorized risk factors. The outcomes in this model were mortality incidence and time to death.
- The significance of parameter estimates derived from the Cox's proportional hazards model was tested with the likelihood ratio statistics.
- The assumptions of the proportional hazards model for the levels of each risk factor was checked by evaluating the linearity of plots of $\log\{-\log[S(t_{i)},_j]\}$describes the *j*th survival time for the *I* level(i=1,2) for each risk factor.
- In further analysis, baseline BMD, rate of bone loss, weight loss, weight fluctuation, age, lifestyle and concomitant diseases were simultaneously considered in a multivariate Cox's proportional hazards model.
- Colinearity was also studied using previously published methods. The plots of martingale residuals against covariates were used to detect nonlinearity.
- Continuous variables included in the final multivariate model were categorized if their effects on the hazard function were nonlinear.
- The Akaike information criterion (AIC) was used to select the best fit model.
- Because each hazard ratio is subjected to sampling variability (as represented by CI), it was also of interest to estimate the posterior probability that an association with a hazard ratio at a cut-point for defining "effect." In this study, the cut-point was selected as 1.2.
- To quantify the contribution of the risk factors, the partial population attributable risk (PAR_p) was estimated for each of the significant risk factors.
- All statistical analyses were performed with SAS and the R statistical environment.

Data Collection Summary:

Timing of Measurements

- All-cause mortality was recorded annually between 1989-2004.
- BMD at the femora; neck was measured by DXA (GE-LUNAR) at baseline and approximately every 2 years afterward.

Dependent Variables

- Ascertainment of mortality during the follow-up period between 1989 and 2004, all deaths and dates of death were recorded.

Independent Variables

- Ascertainment of fractures:
  - First incident nontraumatic and non pathological fractures were considered a risk factor in this study.
  - Fractures occurring during the study period identified for residents of Dubbo local government area through radiologists' reports from the two centers providing x-ray services previously described.
- Clinical data
  - Individuals were interviewed by a nurse coordinator who administered who administered a structured questionnaire data including age, lifestyle factors such as duration of smoking and alcohol consumption, physical activity, any history of fractures in the past.
  - Anthropometric variables (height, weight) were measured, and a dietary assessment was performed based on a frequency questionnaire for calcium intake.
  - Information on concomitant diseases, including cardiovascular disease (CD), all types of cancer, and type I/II diabetes mellitus was also recorded based on the participant's self-report.
- BMD measurements BMD (g/cm^2 was measured at the lumbar spine and femoral neck by DXA using a LUNAR DPX densitometer (GE-LUNAR, Madison, WI, USA).
  - The radiation dose with this method is <0.1μGY.
  - The coefficient of reliability of BMD in the institution in normal subjects is 0.96 and 0.98 at the proximal femur and lumbar spine, respectively.
  - Based on actual measurement of femoral neck BMD(FNBMD), each subject was classified as "osteoporotic" with a BMD being 2.5 SD or more below the young normal level, "osteopenic" with a BMD between 2.5 and 1.1 S.D. below the young normal level, or as "normal." T-scores for the FNBMD were calculated using the Australian BMD reference range.

Control Variables

- Sex (male, female)

Description of Actual Data Sample:

Initial N: 1703 (1059 women; 644 men)

Attrition (final N):1703

Age: ≥ 60 years of age (as of 1989)

Ethnicity: White background

Other relevant demographics:

Anthropometrics

Location:New South Wales (Australia)

Summary of Results:

Key Findings

- In the multivariate Cox's proportional hazards model with adjustment for age, incident fractures, and concomitant diseases, the following variables were independent risk factors of all-cause mortality in men: rate of BMD loss of at least 1%/yr, rate of weight loss at least 1%/yr, and weight fluctuation (defined by CV) of at least 3%.
- In women, in addition to the significant factors observed in men, lower baseline BMD was also an independent risk factor of mortality.
- Approximately 36% and 22% of the deaths in women and men, respectively, were attributable to the four risk factors.

Table 1. Characteristics of Study Participants

Variables	Alive	Deceased	Diff.	(95% CI)	P
Men					
Age(yr)	67.8±5.1	72.2±6.3	-4.3	(-5.2,-3.4)	0.0000
Weight(kg)	79.1±12.1	77.9±12.6	1.2	(-0.7,3.2)	0.2239
Weight loss(% /yr)	0.27±2.68	-0.60±1.65	0.87	(0.50,1.24)	0.0000
Weight fluctuation (%)	3.47±2.36	4.20±3.08	-0.74	(-1.16,-0.31)	0.0007
Height(cm)	173.9±6.6	173.0±6.5	0.9	(-0.2,1.9)	0.1024
BMI(kg/m^2)	26±4	26±4	0.2	(-0.4,0.7)	0.5710
FNBMD(g/cm^2)	0.94±0.14	0.90±0.15	0.03	(0.01,0.06)	0.0033
Rate of BMD loss(%/yr)	-0.38±1.15	-0.73±1.96	0.35	(0.11,0.59)	0.0045
Current/ex-smoking(yes)*	221(56.7)	177(69.7)			0.0010
Any fracture(yes)*†	48(12.3)	60(23.6)			0.0000
CVD(yes)*‡	118(30.3)	84(33.1)			0.4520
All types of cancer(yes)*	47(12.1)	30(11.8)			0.9270
Diabetes(type I and II)(yes)*	37(9.5)	30(11.8)			0.3540
Women					
Age(yr)	68.4±5.8	73.9±7.3	-5.5	(-6.3,-4.7)	0.0000
Weight(kg)	66.4±12.1	63.2±12.6	3.2	(1.6,4.9)	0.0001
Weight loss(% /yr)	0.22±1.61	-0.58±2.10	0.80	(0.56,1.04)	0.0000
Weight fluctuation (%)	4.18±2.71	5.09±3.70	-0.91	(-1.32,-0.50)	0.0000
Height(cm)	160.6±6.0	159.1±6.5	1.4	(0.6,2.3)	0.0007

BMI(kg/m^2)	26±5	25±5	0.8	(0.1, 1.4)	0.0153
FNBMD(g/cm^2)	0.80±0.12	0.74±0.14	0.06	(0.04,0.08)	0.0000
Rate of BMD loss(%/yr)	-0.54±1.23	-0.93±2.63	0.40	(0.17,0.63)	0.0008
Current/ex-smoking(yes)*	223(29.1)	88(30.0)			0.7880
Any fracture(yes)*†	222(29.0)	111(37.0)			0.0050
CVD(yes)*‡	153(20.0)	109(37.0)			0.0000
All types of cancer(yes)*	78(10.2)	32(10.9)			0.7240
Diabetes(type I and II)(yes)*	51(6.7)	26(8.9)			0.2140

Values are mean ±SD, unpaired t-test, unless otherwise specified.
*n (%), X^2 test
† Any fracture, any first incident fracture.
‡ CVD, cardiovascular diseases, including congestive heart failure, ischemic heart disease, myocardial infarction, chronic atrial fibrillation, pulmonary edema.

Table 2. Hazard Ratio of Bone Loss, Weight Loss, Weight Fluctuations, and Other Factors for All-Cause Mortality

		Unadjusted		Age-adjusted	
Variables	Unit of Comparison	HR	(95%CI)	HR	(95%CI)
Men					
Age	+5 yr	**1.7**	**(1.6,1.9)**		
Weight	-10kg	**1.1**	**(1.0,1.2)**	**1.1**	**(1.0,1.2)**
Weight loss	+2%/yr	**2.0**	**(1.7,2.4)**	**1.7**	**(1.4,2.0)**
Weight fluctuation	+3%	**1.2**	**(1.1,1.4)**	**1.2**	**(1.1,1.4)**
Height	-5cm	**1.1**	**(1.0,1.2)**	**1.1**	**(1.0,1.2)**
BMI	-5kg/m^2	1.0	(0.9,1.2)	0.8	(0.70,1.0)
Baseline FNBMD	-0.12 g/cm^2	**1.2**	**(1.1,1.4)**	1.1	(0.9,1.2)
Bone loss	+5%/yr	**2.5**	**(1.6,3.9)**	**1.6**	**(1.1,1.25)**
Ever smoking*	Yes	**1.6**	**(1.2,2.1)**	**1.6**	**(1.2,2.1)**
Any fracture†	Yes	**1.9**	**(1.4,2.5)**	**1.3**	**(1.0,1.8)**
CVD‡	Yes	1.1	(0.9,1.5)	1.1	(0.8,1.4)
All types of cancer	Yes	0.9	(0.6,1.4)	1.0	(0.7,1.5)
Diabetes(type I and II)	Yes	1.2	(0.8,1.7)	1.3	(0.9,1.9)
Women					
Age	+5 yr	**1.8**	**(1.7,2.0)**		
Weight	-10kg	**1.2**	**(1.1,1.4)**	**1.1**	**(1.0,1.2)**
Weight loss	+2%/yr	**1.4**	**(1.3,1.5)**	**1.3**	**(1.2,1.5)**
Weight fluctuation	+3%	**1.2**	**(1.1,1.4)**	**1.2**	**(1.1,1.3)**
Height	-5cm	**1.3**	**(1.1,1.4)**	**1.1**	**(1.0,1.2)**
BMI	-5kg/m^2	**1.1**	**(1.0,1.3)**	1.0	(0.9,1.1)
Baseline FNBMD	-0.12 g/cm^2	**1.5**	**(1.4,1.7)**	**1.3**	(1.1,1.4)
Bone loss	+5%/yr	**2.3**	**(1.7,3.2)**	**1.8**	(1.2,2.5)
Ever smoking*	Yes	1.1	(0.8,1.4)	**1.3**	(1.0,1.7)

Any fracture†	Yes	**1.4**	(1.1,1.8)	**1.4**	(1.1,1.8)
CVD‡	Yes	**2.0**	(1.6,2.6)	**1.5**	(1.2,2.0)
All types of cancer	Yes	1.2	(0.8,1.4)	1.1	(0.8,1.6)
Diabetes(type I and II)	Yes	1.4	(0.9,2.1)	**1.7**	(1.1,2.6)

Bold numbers represent statistical significance at P<0.05 level.
* Ever smoking, current, or ex-smoking vs. nonsmoking.
†Any fracture, any first incident fracture.
‡ CVD, cardiovascular disease, including congestive heart failure, ischemic heart disease, myocardial infarction, chronic atrial fibrillation, pulmonary edema.

Table 3. Independent Risk Factors for All-Cause Mortality (Multivariate Cox's Proportional Hazards Model).

	HR	(95%CI)	Probability that HR≥1.2
Men			
Baseline FNBMD			
Normal	1.0		
Osteopenia	0.9	(0.7,1.2)	0.02
Osteoporosis	1.2	(0.8,1.8)	0.57
Rate of bone loss			
<0.5%/yr	1.0		
0.5-0.9%	0.8	(0.5,1.1)	0.01
≥1%	**1.3**	**(1.0,1.7)**	0.66
Rate of weight loss			
<0.5%/yr	1.0		
0.5-0.9%	1.3	(0.9,2.0)	0.72
≥1%	**2.6**	**(1.9,3.7)**	1.00
Weight fluctuation			
<3%	1.0		
≥3%	1.5	**(1.0,2.1)**	0.91
Women			
Baseline FNBMD			
Normal	1.0		
Osteopenia	0.8	(0.5,1.1)	0.00
Osteoporosis	**1.5**	**(1.0,2.1)**	0.86
Rate of bone loss			
<0.5%/yr	1.0		
0.5-0.9%	0.9	(0.6,1.3)	0.05
≥1%	**1.3**	**(1.0,1.7)**	0.70
Rate of weight loss			
<0.5%/yr	1.0		
0.5-0.9%	1.2	(0.8,1.7)	0.45
≥1%	**2.2**	**(1.7,2.9)**	1.00
Weight fluctuation			

<3%	1.0		
≥3%	**1.3**	**(1.0,1.7)**	0.66

Variables included in the multivariate model were baseline BMD, rate of bone loss, rate of weight loss, weight fluctuations, age, smoking status, and concomitant disease (i.e. incident fracture, cardiovascular diseases, all type of cancers, and type I/II diabetes mellitus).
Posterior probability of HR≥1.2 was computed from the Bayesian analysis, in which the prior information was given a uniform distribution (i.e., nonuniformed prior).
Bold numbers represent statistical; significance at the p>0.05 level.
Table 4. Population Attributable risk Fraction $(PAR)_p$ of Risk Factors for All-Cause Mortality

	PAR_p (%)	(95% CI)
Men		
Osteoporotic BMD(T-scores≤-2.5)	2.5	(-0.5,5.5)
Rate of bone loss(>1%/yr)	6.5	(1.1, 12.0)
Rate of weight loss(>1%/yr)	11.6	(0.5,17.9)
Weight fluctuation (>3%)	1.4	(0.0,5.1)
Total	22.0	
Women		
Osteoporotic BMD(T-scores≤-2.5)	11.1	(5.6,q6.7)
Rate of bone loss(>1%/yr)	10.5	(4.4,16.7)
Rate of weight loss(>1%/yr)	10.9	(5.2,16.5)
Weight fluctuation (>3%)	3.4	(0.0, 7.8)
Total	35.9	

Partial population attributable risks were computed under the condition of multiple risk exposures with adjustment for age and concomitant diseases, including any osteoporotic fracture, cardiovascular diseases, all-cause cancer, diabetes mellitus, and smoking.

Author Conclusion:

- These data suggest that, although low BMD was a risk factor of mortality in women, it was not a risk factor for mortality in men.
- However, high rates of BMD loss, weight loss, and weight fluctuations were also independent predictors of all-cause mortality in elderly men and women, independent of age, incident fracture, and concomitant diseases.

Reviewer Comments:

Authors note the following limitations:

- *The population is of a white background; therefore, extrapolation to other populations should be made with caution.*
- *Selection bias was likely to be present in this study, in that participants were healthier than nonparticipants.*
- *For instance although the relative distribution of subjects with respect to age in the sample was comparable with that in the target population, the mortality rate in the sample was lower than in the general population, which might reflect the bias toward healthy subjects in the study.*

- *Therefore, these results may underestimate, rather than overestimate, the effects of BMD and weight change on mortality.*
- *The causes of death in this study were not defined; therefore it is not possible to make reference regarding the causal link between BMD and weight change and mortality.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	No
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes

3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes

6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A

	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
	8.6.	Was clinical significance as well as statistical significance reported?	Yes
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes